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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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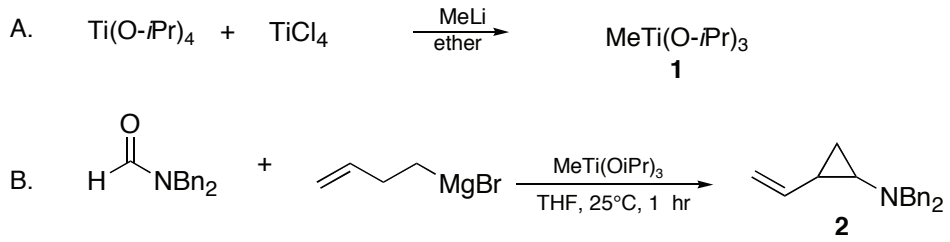
FACILE SYNTHESES OF AMINOCYCLOPROPANES: *N,N*-DIBENZYL-*N*-(2-ETHENYLCYCLOPROPYL)AMINE [(Benzenemethanamine, *N*-(2-ethenylcyclopropyl)-*N*-(phenylmethyl)-]



Submitted by Armin de Meijere, Harald Winsel, and Björn Stecker.[1]
Checked by Fanglong Yang, Sivaraman Dandapani, and Dennis P. Curran.

1. Procedure

A. Methyl tris(isopropoxy)titanium.[2] A 500-mL, three-necked, round-bottomed flask equipped with two rubber septa and a dropping funnel fitted with an argon inlet is charged with a mixture of 44.4 mL (150 mmol) of titanium tetraisopropoxide (Note 1) in 50 mL of anhydrous ether and cooled to 0° C in an ice bath. Titanium tetrachloride (5.49 mL, 50 mmol) (Note 1) is added dropwise via syringe pump over 30 min. The resulting mixture is allowed to warm to room temperature and stirred for 2 h. The reaction mixture is then cooled to 0° C and 123 mL (197 mmol) of a 1.6M solution of methyllithium in ether (Note 1) is added via the dropping funnel over 40 min. The mixture is allowed to warm to room temperature and stirred for 1 h. The dropping funnel is replaced with a short path distillation head, and the ether is removed by distillation at ambient pressure. Distillation of the crude product at reduced pressure (bp 56-57° C, 60 mm) gives 38.5 g (80%) of $MeTi(O\textit{i}Pr)_3$ as a yellow oil (Note 2).

B. N,N-Dibenzyl-N-(2-ethenylcyclopropyl)amine. An oven-dried, 250-mL, three-necked, round-bottomed flask containing a magnetic stirbar and equipped with two rubber septa and an addition funnel fitted with a nitrogen inlet is charged with a solution of 9.0 g (40 mmol) of *N,N*-dibenzylformamide (Notes 3 and 4) in 10 mL of anhydrous tetrahydrofuran (Note 5). $MeTi(O\textit{i}Pr)_3$ (11.5 g, 48 mmol, 1.2 equiv) is added in one portion by syringe, and then 3-butenylmagnesium bromide (1.48M in THF, 40.5 mL, 60 mmol, 1.5 equiv) (Notes 6, 7) is added dropwise via the addition funnel over 30 min. The resulting black suspension is stirred at ambient temperature for an additional hour (Note 8), and the reaction is then quenched by slow addition of 50 mL of diethyl ether followed by 5 mL of water. The mixture is vigorously stirred for 1 h (Note 9), filtered, and the colorless precipitate is then washed with two 20-mL portions of ether. The combined organic phases are washed with 30 mL of brine and dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure (Note 10) to afford 9.4 g of **2** (1:7 ratio of *cis*- and *trans*-isomers) as a deep yellow oil (Notes 11, 12). This crude product is purified by flash chromatography on 350 g of silica gel (200-400 mesh, elution with 100:1 pentane/ether) (Notes 13, 14) to yield 0.73 g (7%) of the *cis*-diastereomer, 0.51 g (5%) of a mixed fraction, and 6.2 g (59%) of the *trans*-diastereomer of 2, each as a pale yellow oil (Notes 15, 16).

2. Notes

1. [MeTi(O*i*Pr)$_3$] must be used in pure form rather than as a solution in hexane. Titanium tetraisopropoxide (95%) was obtained from ABCR, Karlsruhe by the submitters and from Aldrich Chemical Company by the checkers and was distilled under nitrogen before use. Titanium tetrachloride (>99%) was purchased from VWR by the submitters and from Aldrich Chemical Company by the checkers and was used without further purification. The submitters obtained a solution of methyllithium in ether (1.6M, 5 wt%) from Fluka. The amount of titanium tetrachloride was incorrectly given as 6.48 mL and the concentration of methylithium solution was incorrectly given as 1.0 M in the original published version of this *Organic Syntheses* procedure due to typographical errors.

2. The product is air and moisture sensitive, and the checkers used it immediately after preparation. The submitters report that MeTi(O*i*Pr)$_3$ can be stored for several months in a freezer under an inert atmosphere.

3. Other *N,N*-dialkylformamides including commercially available *N*-methylformanilide, *N*-formylmorpholine, *N*-formylpiperidine, *N,N*-diethylformamide and *N,N*-dimethylformamide (DMF) can be employed with essentially the same procedure. With *N,N*-dimethylformamide, care has to be exercised because of the volatility of the product, which can be purified by distillation or chromatography of its hydrochloride salt.

4. *N,N*-Dibenzylformamide was prepared as follows. A 250-mL, round-bottomed flask equipped with reflux condenser fitted with an argon inlet was charged with 100 mL of DMF, 40.4 mL (210 mmol) of dibenzylamine, and 12.8 mL (300 mmol) of formic acid. The solution was heated at reflux overnight, allowed to cool to room temperature, and then quenched by carefully adding 40 mL of saturated Na_2CO_3 solution. The aqueous phase was separated and extracted with four 50-mL portions of ether, and the combined organic layers were washed with two 20-mL portions of brine, dried over $MgSO_4$, and concentrated by rotary evaporation at reduced pressure. The crude product was crystallized from 100 mL of 70:30 ether/pentane to yield 40.2 g (85%) of *N,N*-dibenzylformamide, mp 50-51° C; it is hygroscopic and must be dried before use under reduced pressure (0.007 mm) overnight.

5. The submitters used THF that was freshly distilled from sodium, while the checkers used THF that was dried by pressure filtration through activated alumina.

6. 3-Butenylmagnesium bromide is prepared as follows. A 250-mL, three-necked, round-bottomed flask containing a magnetic stirbar and equipped with two rubber septa and an addition funnel fitted with an argon inlet was charged with 4.8 g (200 mmol) of magnesium turnings (Aldrich) suspended in 70 mL of anhydrous THF. A solution of 18.3 mL (180 mmol) of 4-bromo-1-butene (Aldrich) in 60 mL of anhydrous THF was added by dropping funnel at a rate adjusted to maintain a gentle reflux (total addition time, ca. 3 h). The reaction mixture was then stirred for an additional hour. To determine the concentration of product, a 1-mL aliquot of the mixture was quenched with 0.1N HCl and then back-titrated with 0.1N NaOH (phenolphthalein indicator) which indicated a concentration of 1.5M.

The concentration of the Grignard reagent should not be higher than 1.5M. The use of more concentrated solutions leads to lower yields. Because of the rather high concentration of the reagents, it is important to stir the reaction mixture vigorously during and after the addition of the Grignard reagent. If the reaction is carried out on a larger scale than that described here, then the use of a mechanical stirrer is recommended.

7. The submitters used a syringe pump to add the Grignard solution. However, the checkers experienced problems with precipitation of the Grignard reagent and recommend the use of an addition funnel. If the reagent begins to precipitate in the funnel during the addition period, then gentle warming with a heat gun accomplishes redissolution.

8. The reductive cyclopropanation reaction proceeds very rapidly. For example, the submitters report that hydrolysis of the reaction mixture after only 1 min gives the product in 75% yield. However, stirring for an additional 1 h is recommended, and this should be sufficient for analogous transformations with other Grignard reagents and formamides as well. Higher *N,N*-dialkylcarboxamides may require longer reaction times (up to 5 h).

9. The hydrolysis should be carried out with access of air so that the black titanium(II) derivatives are oxidized rapidly and completely to colorless titanium(IV) compounds.

10. The solvents are removed within 1 h at a bath temperature of 50° C at 15 mm.

11. The *cis/trans* diastereomeric ratio is determined by integration of resonances in the ^{1}H NMR spectrum of the crude mixture and is usually found in the range of 1/6.0 to 1/7.5.

12. TLC analysis of the crude product (elution with 50:1 pentane:ether, visualization with iodine) showed three non-baseline spots: R_f 0.65 (*cis* isomer), R_f 0.52 (unknown impurity), and R_f 0.32 (*trans* isomer). The unknown impurity is intensely sensitive to iodine and largely coelutes with the *cis*-isomer in the subsequent column chromatography. However, the ^{1}H NMR spectrum of this isomer shows excellent purity despite the presence of this spot on TLC. In 100:1 pentane:ether, R_f values of the *cis* and *trans* isomers are about 0.50 and 0.15, respectively.

13. It is important to wet-pack the column with the eluting solvent. Dry packing results in strong retention of the sample and poor separation, possibly because the small amount of ether in the eluting solvent is adsorbed by the dry silica gel.

14. If separation of the diastereomers is not required, then filtration of the crude product through a pad of 50 g of silica eluting with dichloromethane followed by concentration affords a mixture of diastereomers separated from baseline materials.

15. The submitters report obtaining 1.29 (12%) of the *cis*-diastereoisomer and 8.39 g (80%) of the *trans*-diastereoisomer. The submitters recommend that the purified diastereomers be stored in the freezer (-18° C). Both pure isomers slowly equilibrate to a 21:79 mixture of cis/trans isomers upon standing at ambient temperature for several weeks.

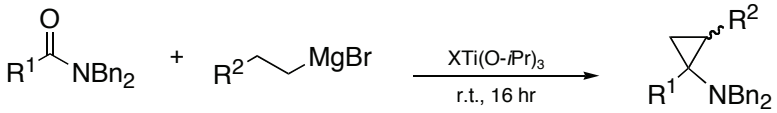
16. The products exhibit the following spectroscopic properties: *trans* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.60 (ddd, J = 6.7, 5.5, 4.9 Hz, 1 H), 0.76 (ddd, J = 9.0, 4.6, 4.6 Hz, 1 H), 1.35-1.26 (m, 1 H), 1.79 (ddd, J = 7.1, 4.2, 3.0 Hz, 1 H), 3.60 (d, J = 13.5 Hz, 2 H), 3.70 (d, J = 13.5 Hz, 2 H), 4.83-4.76 (m, 2 H), 5.33 (ddd, J = 17.0, 10.3, 8.5 Hz, 1 H), 7.34-7.20 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 25.5, 45.1, 58.2, 112.2, 126.8, 128.0, 129.4, 138.4, 139.6; IR cm^{-1}: 3062, 3027, 2921, 2809, 1635, 1493, 1453, 1364. *cis* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.45 (ddd, J = 4.8, 4.8, 4.8 Hz, 1 H), 0.87 (ddd, J = 8.6, 6.8, 4.9 Hz, 1 H), 1.57-1.51 (m, 1 H), 2.06 (ddd, J = 6.8, 6.8, 4.6 Hz, 1H), 7.34-7.22 (m, 10 H), 3.51 (d, J = 13.7 Hz, 2

H), 3.74 (d, J = 13.7 Hz, 2 H), 4.97 (dd, J = 10.3, 2.0 Hz, 1 H), 5.14 (dd, J = 17.3, 2.0 Hz, 1 H), 5.88 (ddd, J = 17.3, 10.3, 9.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6, 23.3, 42.4, 57.2, 113.60, 126.8, 128.0, 129.5, 138.3, 138.4; IR cm^{-1}: 3062, 3026, 2922, 2807, 1634, 1493, 1453, 1364.

3. Discussion

The transformation of *N,N*-dialkylcarboxamides with low valent titanium compounds formed in situ from Grignard reagents and titanium alkoxides of the type $XTi(O\textit{i}Pr)_3$ (X = O*i*Pr, Cl, Me) to correspondingly substituted *N,N*-dialkylcyclopropylamines has been thoroughly examined in recent years since it was first discovered.[3] Related to the conversion of esters to cyclopropanols,[5] this new and reasonably general access to this important class of compounds[4] is now easily carried out and generally furnishes high yields.[6] For example, unsubstituted *N,N*-dialkylcyclopropylamines are obtained from *N,N*-dialkylformamides and ethylmagnesium bromide following this protocol in up to 98% yield.

Scheme 1. Generality of the titanium mediated reductive cyclopropanation of *N,N*-diakylcarboxamides. More than 60 compounds have been prepared by this route.



entry	R^1	R^2	yield (%)	*cis/trans*
1	H	H	98	—
2	H	*n*Bu	90	1 : 2.0
3	H		85	1 : 2.2
4	H	Ph	92	1 : 2.0
5	H		92	1 : 7.0
6	Me	H	77	—
7	Et	H	70	—

$R^1 = R^2$ = H, Alkyl, Alkenyl, Aryl, functionally substituted Alkyl, Alkenyl, Aryl
X = Me, Cl, O*i*Pr

The products can be purified by distillation or crystallization as hydrochloride salts, but they can often be used for subsequent transformations without purification.

The best titanium mediator appears to be methyltitanium triisopropoxide, yet good yields are also obtained with titanium tetraisopropoxide and chlorotitanium triisopropoxide. The methyl group on titanium serves as a dummy alkyl ligand which is eliminated as methane after hydride transfer from the other alkyl group introduced from the Grignard reagent so that essentially only one equivalent of the latter would be required. However, yields do increase from 80-85% to over 90% in most cases by using an excess of the Grignard reagent (up to 2.5 equiv.). In the presence of titanium tetraisopropoxide and with the use of more than two equivalents of the Grignard reagent, the desired product is usually obtained from an *N,N*-dialkylformamide in over 80% yield along with 10-15% of the corresponding dialkylamine.

The reaction is best performed in THF. In less polar solvents such as diethyl ether or benzene, the chemical yields are significantly lower.

In the presence of 1 equiv. of chlorotrimethylsilane, the transformation can be performed with substoichiometric amounts of titanium tetraisopropoxide (25 mol%) to yield 73% of the diastereomeric mixture of the corresponding *N,N*-dialkylaminocyclopropane.[7]

Ethenylcyclopropylamines such as the described one are essentially functionally substituted cyclopropylamines, since the ethenyl group can easily be converted to functionally substituted ethyl groups, e. g., by hydroboration/oxidation or hydroboration/amination, and eventually the benzyl groups can be removed by catalytic hydrogenation to yield the corresponding primary cyclopropylamines. Ethenylcyclopropylamines can also easily be transformed to cyclopenten-4-ylamines by thermal rearrangement.[3c] Functionality can also directly be introduced with the carboxamide,[8a] the Grignard reagent,[8b] or the use of functionalized organozinc reagents.[8c]

A wide range of alkenyl-, aryl-, alkyl-, and dialkyl-substituted cyclopropylamines can be made by reaction of an *N,N*-dialkylformamide (or higher *N,N*-dialkylcarboxamide) with cyclohexylmagnesium halide in the presence of methyltitanium triisopropoxide (or titanium tetraisopropoxide) and a 1,3-diene, a styrene, a terminal or an internal alkene following this protocol with some minor modifications.[9] In these cases the reacting low valent titanium intermediate is generated by ligand exchange,[10] and the overall transformation corresponds to an aminocyclopropanation of the added alkene. For example, a solution of *N*-Boc-protected pyrroline (4.36 g, 25.8 mmol) and $Ti(O\textit{i}Pr)_4$ (9.06 mL, 30.9 mmol) in THF (100 mL) is treated with MeMgCl (10.3 mL of a 3M solution in THF, 30.9 mmol, added within 10 min) at 0° C and the mixture is warmed to ambient temperature. *N,N*-Dibenzylformamide (6.95 g, 30.9 mmol) is added in one portion, then dropwise with stirring a solution of cyclohexylmagnesium bromide (28.1 mL of a 2.2M solution in diethyl ether, 61.9 mmol) within 2 h. The mixture is heated under reflux for an additional 1 h, then cooled to ambient temperature. Addition of 100 mL of water and 100 mL of pentane, filtration and further workup with filtration through a pad of 10 g of basic aluminum oxide and subsequent crystallization from pentane yields 8.75 g (90%) of crystalline *N*-Boc-protected *exo*-6-*N,N*-dibenzylamino-3-azabicyclo [3.1.0] hexane.[9b]

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2. Reetz, M. T.; J. Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421-1440.

3. (a) Chaplinski, V.; de Meijere, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 413-414. (b) Chaplinski, V.; Winsel, H.; Kordes, M.; de Meijere, A. *Synlett* **1997**, 111-114. (c) Willliams, C. M.; de Meijere, A. *J. Chem. Soc., Perkin Trans.* **1998**, 3699-3702. (d) Kordes, M.; Winsel, H.; de Meijere, A. *Eur. J. Org. Chem.* **2000**, 3235-3245.

4. Salaün, J. *Topics in Current Chemistry* **2000**, *207*, 1-67.

5. Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244-2245; *J. Org. Chem. USSR (Engl. Transl.)* **1989**, *25*, 2027-2028.

6. Reviews: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789-2834. (b) de Meijere, A.; Kozhushkov, S. I.; Savchenko, A. I. in *Titanium and Zirconium in Organic Synthesis*, (Ed.: I. Marek), Wiley-VGH, Weinheim, **2002**, 390-434.

7. de Meijere, A.; Stecker, B., to be published. Stecker, B., Dissertation, Universität Göttingen, 2002.

8. (a) Winsel, H.; Gazizova, V.; Kulinkovich, O.; Pavlov, V.; de Meijere, A. *Synlett* **1999**, 1999-2003. (b) Winsel, H. Dissertation Universität Göttingen, 2000. (c) Wiedemann, S.; Marek, I.; de Meijere, A. *Synlett.* **2002**, 879-882.

9. (a) Williams, C. M.; Chaplinski, V.; Schreiner, P. R.; de Meijere, A. *Tetrahedron Lett.* **1998**, *39*, 7695-7698. (b) de Meijere, A.; Williams, C. M.; Chaplinski, V.; Kourdioukov, A.; Sviridov, S. V.; Savtchenko, A.; Kordes, M.; Stratmann, C. *Chem. Eur. J.* **2002**, *8*, 3789-3801.

10. (a) Lee, J. C.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 1584-1585. (b) Lee, J. C.; U, J. S.; Blackstock, S. C.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 10241-10242. (c) Lee, J. C.; Sung, M. J.; Cha, J. K. *Tetrahedron Lett.* **2001**, *42*, 2059-2061.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N,N-Dibenzyl-*N*-(2-ethenylcyclopropyl)amine: Benzenemethanamine, *N*-(2-ethenylcyclopropyl)-*N*-(phenylmethyl)-; (220247-75-5)

N,N-Dibenzylformamide: Formamide, *N,N*-bis(phenylmethyl)-; (5464-77-7)

Dibenzylamine: Benzenemethanamine, *N*-(phenylmethyl)-; (103-49-1)

Formic acid; (64-18-6)

Methyl tris(isopropoxy)titanium: Titanium, methyltris(2-propanolato)-, (T-4)-; (18006-13-8)

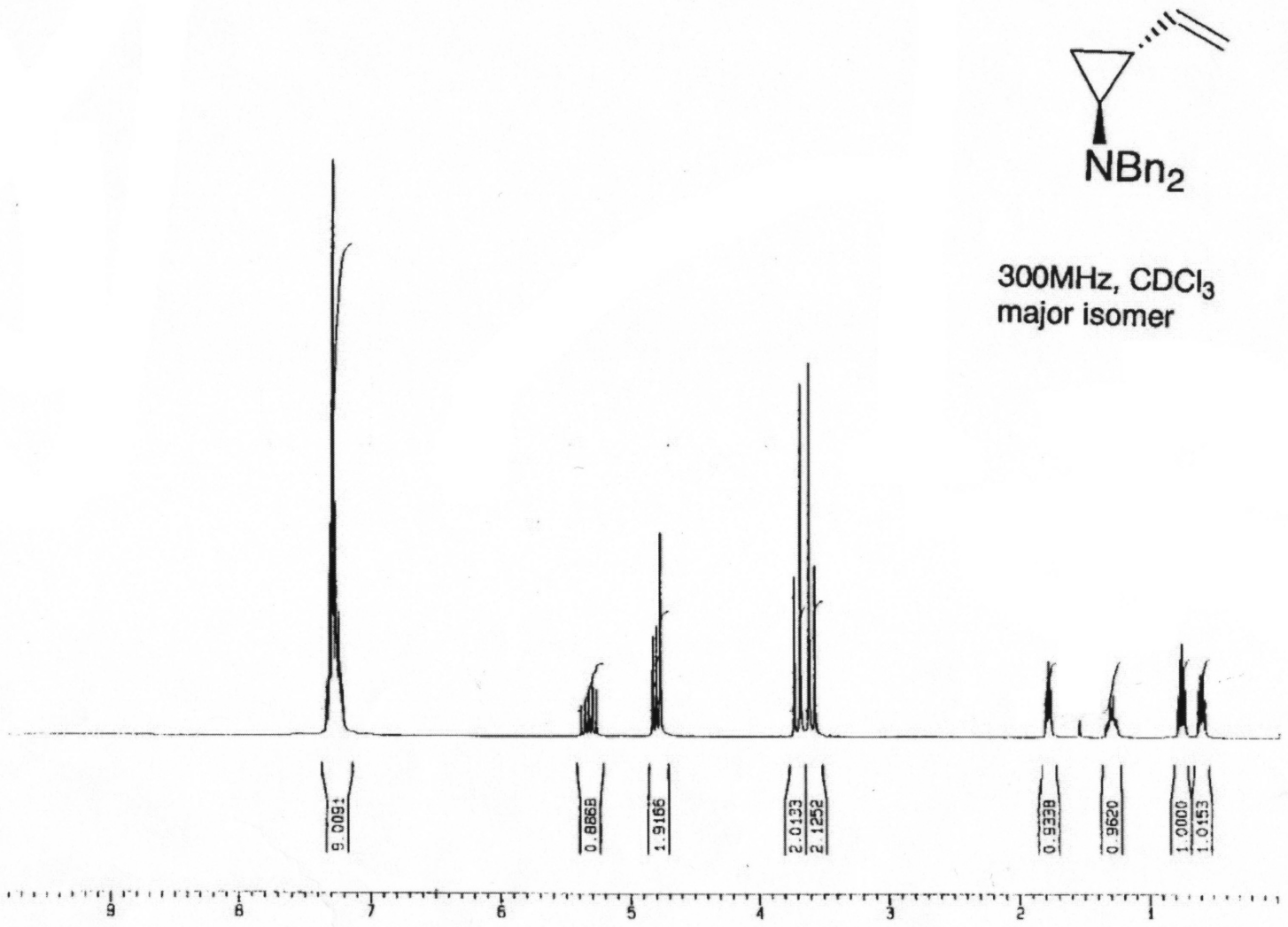
Titanium tetraisoproproxide: 2-Propanol, titanium (4+)salt; (546-68-9)

Titanium tetrachloride: Titanium chloride ($TiCl_4$)(T-4) (9); (7550-45-0)

Methyllithium: Lithium, methyl-; (917-54-4)

4-Bromo-1-butene: 1-Butene, 4-bromo-; (5162-44-7)

3-Butenylmagnesium bromide: Magnesium, bromo-3-butenyl-; (7013-09-5)


NBn2
300MHz, CDCl3
major isomer
9.0091
0.8868
1.9166
2.0133
2.1252
0.9338
0.9620
1.0000
1.0153
9
8
7
6
5
4
3
2
1